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10/618,088	07/14/2003	Elizabeth Jaffee	001107.00363	4098

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,088	JAFFEE ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-38,111 and 113-115* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-24,26-38,111 and 113-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 22- 38, 111, and 113-115 are all the pending claims for this application.

2. Claims 1-21, 39-110 and 112 were cancelled, Claims 22, 29 and 35-38 were amended to replace the term "vaccine" with "composition", and new claims 113-115 were added in the Response of 4/30/07.

3. Claim 25 is withdrawn from examination.

4. Claims 22-24, 26-38, 111 and 113-115 are all the pending claims under examination.

5. This action is **FINAL**.

Withdrawal of Objections

Specification

6. The objection to the specification for failing to include sequence identifiers for the sequences disclosed in Table 1, [29], [23], and [132] pursuant to 37 CFR 1.821 (c) and/or (d) is withdrawn in view of the amendments to the specification described on pp. 4-7 of the Response of 4/30/07.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of Claims 22-24, 26-38 and 111 (and new claims 113-115) under 35 U.S.C. 112, first paragraph, in lacking enablement is maintained for reasons of record as set forth in the Office Action of 10/30/06 and herein below.

Applicants' allegations set forth on pp. 8-11 in the Response of 4/30/07, the Declaration of Dr. Jaffee, the exhibits attached thereto and the interview of March 14, 2007 have been considered but are not found persuasive in enabling the full scope of the instant claims.

Applicants have not demonstrated with a preponderance of corroborating or convincing evidence that any form of DNA encoding the mesothelin protein comprising any one or more of the inventive peptides when administered to a human patient would in fact provide "efficacy" insofar as increasing survival or improving life expectancy by inducing an MHC-specific and CTL-specific response to an epitope of the mesothelin protein, regardless of what form the DNA is administered, e.g., naked vector, adenoviral vector composition, an expressed recombinant protein on a *Lysteria monocytogenes* bacterium, etc.

WF-3 animal model

a) Applicants were the first to describe the WF-3 animal model in Examples 6-11 of the specification. WF-3 as discussed during the interview of March 14, 2007 is a mesothelin-expressing cell line and *not a pancreatic cancer cell line*. Applicants stated on the record, that there is no known model for a human mesothelin-expressing pancreatic cancer and that the cell line was modified to create a high level, mesothelin-

expressing model. WF-3 cells do not appear to invade the pancreas but grow in the peritoneum as ascites of adoptive C57BL/6 mice.

Significantly, Applicants allege on p. 10, lines 4-5 of the Response of 4/30/07 "Induction of mesothelin-specific cytotoxic T lymphocytes is not specifically shown in this model." Instead, "The effect is shown by increased survival" (p. 10, line 3). Then in the Jaffee Declaration at [15-19], specifically at [19], Jaffee alleges "the DNA vaccine was shown to be capable of inducing mesothelin-specific T-cell mediated specific lysis of WF-3 cells (Example 11 and Figure11)"..."a mesothelin-encoding DNA vaccine composition can generate mesothelin-specific, antitumor T-cell immune responses in a mammal..." Based on the foregoing, Applicants appear to be drawing distinctly opposite or at least contrasting conclusions about the CTL-inducing effects of the DNA therapy in the WF-3 model. Applicants own interpretation of the results for DNA therapy in the WF-3 animal model is inconclusive.

The DNA therapy appears to provide for increased survival of mice in the WF-3 model although it is not clear if this is under disease-free conditions and what if any other natural mesothelin-expressing cancer the DNA therapy could be used to treat. It is not demonstrated that the DNA therapy induces tumor regression. One skilled in the art could not reasonably extrapolate any of these findings to treating mesothelin-expressing pancreatic tumors in a human patient with any kind of DNA-mesothlin therapy.

Listeria animal model

b) Applicants' Response of 4/30/07 on p. 10 refers to the discussion in the Jaffee Declaration at [20-27] regarding examples of independent studies using Listeria-based mesothelin-encoding vaccines in mouse models.

The Jaffee Declaration summarizes Examples 31B-31D of US2005/0249748 alleges that because the inventive peptides (SEQ ID NO:2-5) are inherent to the mesothelin of US2005/0249748, one of skill in the art would be enabled to practice the inventive method in humans suffering from or having had a tumor removed, especially a pancreatic tumor, using a mesothelin-expressing Listeria monocytogenes bacterium as a delivery vehicle.

The Examiner respectfully disagrees that US2005/0249748 is any more enabling for the inventive method using a recombinant mesothelin-expressing Listeria monocytogenes bacterium because no where in Examples 31B-31D is it shown that a) a xenogenic human pancreatic carcinoma in a mouse model has been tested, b) that the bacterium would induce an epitope specific CTL response in a pancreatic cancer model, c) the composition comprising both a polynucleotide encoding mesothelin and recombinant mesothelin-expressing Listeria monocytogenes would be effective, d) the composition induces tumor regression, and c) the composition keeps the mouse tumor free after removal of the tumor.

At [25-26], the Jaffee Declaration summarizes the studies presented in a poster from a SPORE Meeting (Exhibit 6) which is entitled "CRS-207: Live-attenuated Listeria

monocytogenes encoding mesothelin for immunotherapy of patients with pancreatic and ovarian cancers."

The poster abstract does not show any studies on human pancreatic cancer being treatable with a mesothelin-expressing Listeria monocytogenes bacterium. The only studies described are those in a lung tumor nodule model using the mesothelin-expressing Listeria-based delivery. Thus, the poster abstract is not on point with the instant method claims for a pancreatic cancer.

Further, the instant claims are not drawn to an attenuated or modified bacterium that is otherwise rendered exo- or endotoxin-free, thus it is not understood how one of skill in the art could even practice the method using a composition comprising just any wild-type bacterium much less a Listeria without first producing a detrimental effect such as septic shock in the patient.

Phase I Clinical Trial

c) On pp. 10-11 of the Response of 4/30/07 and in the Jaffee Declaration at [6-11], Applicants discuss the results of a clinical trial with 14 human patients using a whole cell tumor vaccine comprising two GM-CSF- and mesothelin-expressing pancreatic cell lines and administered after the adenocarcinoma of the pancreas had been surgically resected from the patients (Thomas publication, Exhibit 2). The tumor vaccine produced mesothelin-specific CTLs in three of the patients against peptide of SEQ ID NO: 1-6 when PBLs were tested in vitro. Applicants correlate these observations with longterm disease-free survival and post-vaccination in vivo delayed type hypersensitivity (better clinical course) for the three patients.

Notably, the whole tumor vaccine does not in any way resemble the inventive reagent(s) of the instant claims. Thus Applicants have not demonstrated that any polynucleotide (in any form much less a recombinant Listeria monocytogenes) encoding mesothelin much less the inventive peptides would produce any such effects, i.e., induction of mesothelin-specific T cells through MHC class I binding, longterm disease-free survival and in vivo DTH responses to autologous tumor cells, in a human patient that meets all of the instant claims limitations.

Further it is noted that all of the patients had undergone surgery to render them essentially tumor-free (having minimal residual disease [7, line 3] of the Jaffee Declaration) and none of the evidence of record demonstrates efficacy for the inventive method in a human patient with a full, non-resected pancreatic tumor.

Phase II Clinical Trials

d) On p. 11, ¶1 of the Response of 4/30/07 and in the Jaffee Declaration at [12-14], Applicants discuss the results of two Phase II clinical trials using the mesothelin-expressing whole tumor cell approach. Applicants describe induction of mesothelin-specific T cells in about 1/3 of the patients and correlate the prolonged, progression-free survival with the tumor cell approach. While these studies demonstrate that mesothelin is effective as an immune target for pancreatic carcinoma in humans, none of the trials appear to use a method, which even reads on the instant scope of the claims and would allow one of skill in the art to practice the method. None of the clinical trials methods resemble the instant polynucleotide reagents for performing the method MHC Class binding and epitope-specific CTL induction.

Despite Applicants assertions that the body of evidence supports a DNA (polynucleotide)-mesothelin based approach to pancreatic cancer therapy vis-à-vis CTL specific killing of tumor target, Applicants have not shown that any such approach has been or can be practiced in a human patient. For all of these reasons, the rejection of the claimed invention is maintained.

Conclusion

8. No claims are allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/Larry R. Helms/

Supervisory Patent Examiner